

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
18 December 2003 (18.12.2003)

PCT

(10) International Publication Number
WO 2003/103697 A3

- (51) International Patent Classification⁷: **A61K 38/26**,
A61P 3/04, 3/04 // C07K 14/605
- (21) International Application Number:
PCT/EP2003/006207
- (22) International Filing Date: 11 June 2003 (11.06.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
0201783-8 11 June 2002 (11.06.2002) SE
60/387,390 11 June 2002 (11.06.2002) US
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- (81) Designated States (*national*): AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report:
3 June 2004
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: USE OF COMPOUNDS HAVING GIP ACTIVITY FOR THE TREATMENT OF DISORDERS ASSOCIATED WITH ABNORMAL LOSS OF CELLS AND/OR FOR THE TREATMENT OF OBESITY

(57) Abstract: Use of a compound having 50% activity or more of the activity of gastric inhibitory polypeptide, GIP, when tested in the same assay under the same conditions, and/or the use of GIP, analogues and fragments thereof, for the manufacture of a pharmaceutical composition for prophylaxis and/or treatment of conditions caused or characterized by abnormal loss of cells and/or for prophylaxis and/or treatment of over weight and obesity. A compound as described above for the prophylaxis and/or treatment of over weight and obesity. Use of antagonists to GIP or the GIP receptor for the prophylaxis and/or treatment of disorders caused or characterized by hyperproliferation of cells and/or abnormally low body weight. A compound for the manufacture of a composition for prophylaxis and/or treatment of depression and/or mood disorders, and a method for determining the level of GIP in the brain of a mammal, is also included.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/03/06207

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/26 A61P25/00 A61P3/04 //C07K14/605

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, MEDLINE, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 199 21 537 A (HOERSCH DIETER) 23 November 2000 (2000-11-23) column 7; claims 5,8 column 8; claim 19 ---	1-16,31, 32,40
X	DATABASE WPI Section Ch, Week 199320 Derwent Publications Ltd., London, GB; Class A96, AN 1993-164366 XP002258007 & JP 05 097694 A (DENKI KAGAKU KOGYO KK), 20 April 1993 (1993-04-20) abstract --- -/--	1

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

6 February 2004

Date of mailing of the international search report

24.03.2004

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/06207

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LACROIX A: "Recepteurs illicites dans le syndrome de Cushing surrealien" ANNALES D'ENDOCRINOLOGIE, vol. 62, no. 2, 2001, pages 185-188, XP002258002 ISSN: 0003-4266 abstract	17-21
A	--- WO 00 58360 A (FLATT PETER RAYMOND ; HARTE FINBARR PAUL MARY O (GB); UNIV ULSTER ()) 5 October 2000 (2000-10-05) page 33 -page 34, line 14 abstract	1-21,40
X	---	31-33
X	EP 0 479 210 A (SANWA KAGAKU KENKYUSHO CO) 8 April 1992 (1992-04-08) page 3, line 1 - line 6 page 9; claims 1,2	31,32
A	---	1-21,40
X	WO 98 24464 A (UNIV BOSTON) 11 June 1998 (1998-06-11) page 6, line 25 -page 11, line 21 abstract	31-33,40
A	---	22-30, 34-39
A	TRÜMPER A ET AL: "Glucose-dependent insulinotropic polypeptide is a growth factor for beta (INS-1) cells by pleiotropic signaling." MOLECULAR ENDOCRINOLOGY (BALTIMORE, MD.) UNITED STATES SEP 2001, vol. 15, no. 9, September 2001 (2001-09), pages 1559-1570, XP002269317 ISSN: 0888-8809 page 156: left column last 2 sentences	1-21,40
A	--- KAPLAN ANDREW M ET AL: "Gastric inhibitory polypeptide (GIP) binding sites in rat brain" PEPTIDES (TARRYTOWN), vol. 15, no. 2, 1994, pages 297-302, XP002258003 ISSN: 0196-9781 the whole document	1-21,40
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INTERNATIONAL SEARCH REPORT

International Application No

PCT 03/06207

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>COLE S L ET AL: "The identification of glucose insulintropic polypeptide (GIP) in rat sensory ganglia and its regulation by somatostatin" REGULATORY PEPTIDES, vol. 102, no. 1, 15 October 2001 (2001-10-15), page 52 XP002258004 5th International Symposium on VIP, PACAP, Secretin, Glucagon and Related Peptides; Santa Barbara, CA, USA; November 04-08, 2001 ISSN: 0167-0115 left-hand column abstract</p>	1-21,40
A	<p>EL-SALHY M ET AL: "Immunohistochemical investigations of neuropeptides in the brain, corpora cardiaca, and corpora allata of an adult lepidopteran insect, Manduca sexta (L)." CELL AND TISSUE RESEARCH. GERMANY, WEST 1983, vol. 232, no. 2, 1983, pages 295-317, XP002258005 ISSN: 0302-766X abstract</p>	1-21,40
A	<p>R.J. BOLLAG ET AL: "Glucose-dependent insulintropic peptide is an integrative hormone with osteotropic effects" MOLECULAR AND CELLULAR ENDOCRINOLOGY, vol. 177, 2001, pages 35-41, XP002258006 Elsevier Science Ireland Ltd. ISSN: 0303-7207 page 39, right-hand column, last paragraph -page 40, left-hand column, paragraph 1 abstract</p>	1-17
A	<p>EP 0 186 181 A (SYNTEX INC) 2 July 1986 (1986-07-02) column 1, line 27 - line 36 abstract</p>	17-21
A	<p>DIXON K N ET AL: "GASTRIC INHIBITORY POLYPEPTIDE IN ANOREXIA NERVOSA" INTERNATIONAL JOURNAL OF EATING DISORDERS, vol. 4, no. 4, 1985, pages 597-604, XP002269318 ISSN: 0276-3478 abstract</p>	36-39

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/03/06207

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03 030946 A (NOVARTIS AG ;GOLIGHTLY DOUGLAS (US); HUGHES THOMAS (US); SAKHUJA K) 17 April 2003 (2003-04-17) page 1, paragraph 1 page 2, paragraph 3 page 14, paragraph 2 -----	22-40

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 03/06207

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
DE 19921537	A	23-11-2000	DE 19921537 A1	23-11-2000
JP 5097694	A	20-04-1993	JP 3283288 B2	20-05-2002
WO 0058360	A	05-10-2000	AU 3441400 A	16-10-2000
			CA 2367856 A1	05-10-2000
			EP 1171465 A2	16-01-2002
			WO 0058360 A2	05-10-2000
EP 0479210	A	08-04-1992	JP 4145099 A	19-05-1992
			AT 123296 T	15-06-1995
			DE 69110101 D1	06-07-1995
			DE 69110101 T2	29-02-1996
			DK 479210 T3	31-07-1995
			EP 0479210 A2	08-04-1992
			ES 2076437 T3	01-11-1995
WO 9824464	A	11-06-1998	AU 5518798 A	29-06-1998
			US 2002151495 A1	17-10-2002
			WO 9824464 A1	11-06-1998
EP 0186181	A	02-07-1986	AU 586658 B2	20-07-1989
			AU 5160385 A	03-07-1986
			DK 606185 A	25-06-1986
			EP 0186181 A2	02-07-1986
			JP 61180718 A	13-08-1986
WO 03030946	A	17-04-2003	WO 03030946 A1	17-04-2003

INTERNATIONAL SEARCH REPORT

International application No.
T/EP 03/06207

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17, 18, 34, 37 partially
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 1-8, 14-25, 31-33, 35-36, 38-39 all partially
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
1-40
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 17, 18, 34, 37 partially

Claims 17, 18, 34 and 37 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practiced on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds or compositions.

Continuation of Box I.2

Claims Nos.: 1-8, 14-25, 31-33, 35-36, 38-39 all partially

Present claims 1-8 and 14-16 relate to the use of a compound, or the compound per se, this compound being defined by reference to a desirable characteristic or property, namely that the compound, when tested in an in vitro proliferation assay, has an activity that corresponds to a certain percentage of the activity of SEQ ID NO: 2 (GIP). The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. Additionally, previously known compounds may be included in the scope of the present claims. Due to the characterization of the compound, it is almost impossible to compare compounds disclosed in prior art with the scope of the present claims. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compound being GIP, SEQ ID NO: 2 or having a certain sequence identity or similarity to SEQ ID NO: 2.

Present claims 22-25, 31-33 and 35 relate to the use of a compound, or the compound per se, this compound being defined by reference to a desirable characteristic or property, namely that the compound, when tested in an assay wherein rats are given the compound intraventricularly in the brain followed by the recordation of the weight of each rat, has an activity in reducing weight gain that corresponds to a certain percentage of the activity of SEQ ID NO: 2 or 4 (GIP). The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.

Additionally, previously known compounds are included in the scope of the present claims. Due to the characterization of the compound, it is almost impossible to compare compounds disclosed in prior art with the scope of the present claims. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compound being GIP, SEQ ID NOs: 2 or 4 or having a certain sequence identity or similarity to SEQ ID NOs: 2 or 4.

Present claims 1-6, 16 (and thereupon dependent claims) and claims 17-21 relate to an extremely large number of possible uses and compounds due to the very broad wordings regarding the conditions to be treated. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the claimed conditions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been focused on those parts of the claims which appear to be supported and disclosed, namely those parts related to the conditions mentioned in claim 6 and the general aspect of hyperproliferation of cells. Thereto, an attempt has been made to search for the general aspects of abnormal loss of cells.

Present claims 17, 19-21, 36 and 38-39 relate to the use of a compound defined by reference to a desirable characteristic or property, namely that the compound should be an antagonist to GIP or the GIP receptor. The claims cover all compounds having this characteristic or property, whereas the application lacks support for such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the general wording "antagonist" to GIP or the GIP receptor. No specific antagonists have been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-21 and 40 (partially)

Claims 1-21 and 40 (partially), directed to the use of a compound having GIP-activity in the treatment of conditions characterized by abnormal loss of cells, and claims directed to such a compound per se. Also included is the use of antagonists to GIP or the GIP receptor in the treatment of conditions caused or characterized by hyperproliferation of cells.

2. Claims: 22-39 and 40 (partially)

Claims 22-39 and 40 (partially), directed to the use of a compound having GIP-activity in the treatment of overweight and/or obesity, claims directed to such a compound per se. Also included is the use of antagonists to GIP or the GIP receptor in the treatment of conditions caused or characterized by abnormally low body weight.

3. Claim : 41

Claim 41, directed to use of GIP or analogues for the manufacture of a pharmaceutical composition for treatment of depression and/or mood disorders.

4. Claims: 42-45

Claims 42-45 directed to methods for determining GIP in the brain of a mammal.